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PATENT COOPERATION TREATY

AGT.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

DEAN, John Paul et al
WITHERS & ROGERS
Goldings House
2 Hays Lane
London SE1 2HW
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	02.10.2001
Applicant's or agent's file reference: P101142/JPD	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02741	17/07/2000	15/07/1999

Applicant: THE UNIVERSITY OF BRISTOL et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Digiusto, M Tel.+49 89 2399-8162

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P101142/JPD		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02741	17/07/2000	15/07/1999
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant THE UNIVERSITY OF BRISTOL et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/02/2001	02.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Knudsen, H Telephone No. +49 89 2399 8696

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02741

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-18 as originally filed

Claims, No.:

1-38 as originally filed

Drawings, sheets:

1/5-5/5 as originally filed

Sequence listing part of the description, pages:

1-8, filed with the letter of 23.10.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 38(N,IS,IA),7-17,21-23,31-34,36-37 (IA).

because:

☒ the said international application, or the said claims Nos. 7-17,21-23,31-34,36-37 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 38.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02741

1. Statement

Novelty (N)	Yes:	Claims	6,8-12,14-17,20,23,26,28-35
	No:	Claims	1-5,7,13,18-19,21-22,24-25,27,36-37
Inventive step (IS)	Yes:	Claims	
	No:	Claims	6,8-12,14-17,20,23,26,28-35
Industrial applicability (IA)	Yes:	Claims	1-6,18-20,24-30,35
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the opinion

The sequence listing pages 1-8, filed with the letter of 23.10.2000 do not form part of the application (Rule 13ter.1(f) PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 7-17, 21-23 and 36-37, insofar as methylation status is determined in a subject, and claims 31-34 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: MALIK K T A ET AL: 'Identification of an Antisense WT1 Promoter in Intron 1: Implications for WT1 Regulation' ONCOGENE, vol. 11, 1995, pages 1589-1595, ISSN: 0950-9232.

D2: HILTUNEN M O ET AL.: 'Hypermethylation of the WT1 and calcitonin gene promoter regions at chromosome 11p in human colorectal cancer' BRITISH JOURNAL OF CANCER, vol. 76, no. 9, 1997, pages 1124-1130.

D3: LAUX D E ET AL.: 'Hypermethylation of the Wilms' tumor suppressor gene CpG island in human breast carcinomas ' PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 38, 1997, page A1195.

D4: HUANG T H-M ET AL.: 'Identification of DNA methylation markers for human breast carcinomas using the methylation-sensitive restriction fingerprinting technique' CANCER RESEARCH, vol. 57, 1997, pages 1030- 1034.

D5: FEINBERG A P: 'Imprinting of a genomic domain of 11p15 and loss of imprinting in cancer: an introduction' CANCER RESEARCH, vol. 59, 1999, pages 1743s-1746s.

D6: TYCKO B: 'DNA Methylation in Genomic Imprinting' MUTATION RESEARCH, vol. 386, no. 2, 1997, pages 131-140, ISSN: 0027-5107

D7: MOULTON T ET AL.: 'Genomic imprinting and Wilms' tumor' MEDICAL AND PEDIATRIC ONCOLOGY, vol. 27, 1996, pages 476-483.

D8: MOORWOOD K ET AL.: 'Definition of a novel negative regulatory element of the WT1 antisense promoter' ANTICANCER RESEARCH, vol. 18, no. 6C, 1998, pages 4909-4910.

D9: MOORWOOD K ET AL.: 'Antisense WT1 transcription parallels sense mRNA and protein expression in fetal kidney and can elevate protein levels in vitro' JOURNAL OF PATHOLOGY, vol. 185, 1998, pages 352-359.

D10: MALIK K ET AL.: 'Identification and differential methylation of the WT1 antisense regulatory region and relaxation of imprinting in Wilms' tumor' CANCER RESEARCH, vol. 60, 2000, pages 2356-2360.

NOVELTY:

D1 discloses DNA sequences SEQ.1 and SEQ.2 and is therefore novelty destroying for claims 1-5, 18-19.

D2 discloses hypermethylation of the WT1 promoter in human colorectal cancer as determined by genomic sequencing and is therefore novelty destroying for claim 7 and 21-22.

D3 discloses hypermethylation of WT suppressor gene CpG islands in human breast carcinoma as determined with methylation sensitive restriction endonucleases, eg Bss HII and is therefore novelty destroying for claims 7, 13 and 21-22.

D4 suggests that hypermethylation of a region within the antisense promoter in intron 1 of WT1 appears to be common in primary breast carcinomas (see p.1033, right column, 2nd paragraph) and is therefore novelty destructive for claims 21-22.

D5 discloses that a genomic domain of 11p15 loses imprinting and that this is one of the most common genetic disorders found in cancer. A mutation is found to cause loss of imprinting in Wilms' tumour and it is suggested that aberrant DNA methylation may be one of the reasons for the loss of imprinting. Thus, D5 is novelty destroying for claims 24 and 27

D6 discloses that abnormal DNA methylation accompanies the relaxation of imprinting on chromosome 11p15.5 in Wilms' tumours and is therefore novelty destructive for claims 7, 21, 24-25, 27 and 36-37.

INVENTIVE STEP:

The connections between DNA methylation, loss of imprinting and cancer is discussed in a variety of documents, eg D5-D7. The role of the antisense promoter in intron 1 of the WT1 gene in the control of the WT1 gene expression is also discussed in a number of documents, eg D1, D4 and D8-D9. Thus, the claimed subject-matter, against which no novelty objection is raised, does not appear to involve an inventive step as it lies within the scope of what would be obvious to the skilled person in view of the disclosures given in the ample number of relevant documents.

The only finding which would appear to contribute something unobvious to the state of the art is that of present claim 11. However, the present application does not contain sufficient support for this finding and an inventive step can only be acknowledged when it is clear that the technical problem, ie the long-term prognosis, is actually solved by the claimed method.

INDUSTRIAL APPLICABILITY:

For the assessment of the present claims 7-17, 21-23, 31-34 and 36-37 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as

industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

P-DOCUMENTS:

D10 is published before the present application's filing date, but after its priority date and is therefore relevant prior art only to the subject-matter, if any, which does not have a valid claim to priority.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5(a)(ii) PCT, the closest prior art documents D1-D3 are not identified in the description and the relevant background art disclosed therein is not briefly discussed.

Re Item VIII

Certain observations on the international application

The number of independent claims and the variation in essential features mentioned therein is so that it is difficult to determine the exact scope of protection sought by the applicant.